REVIEW

Effects of Polyphenols in a Mediterranean Diet on Symptoms of Depression: A Systematic Literature Review

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ABSTRACT

Depression is a mood disorder which currently affects 350 million individuals worldwide. Recently, research has suggested a protective role of diet for depression. The Mediterranean-style dietary pattern has been highlighted in several systematic reviews as a promising candidate for reducing depressive symptoms. It has been speculated that this could be due to the high polyphenol content of foods commonly found in the diet. Therefore, the aim of this review was to assess the effects of polyphenols found in a Mediterranean diet on the symptoms of depression. A systematic literature review was conducted of original research which assessed the role of polyphenols on the symptoms of depression in humans. The following databases were searched: PROQUEST, SCOPUS (Elsevier), MEDLINE (EBSCO), CINAHL, and EMBase, up to 18 February, 2019. The inclusion criteria consisted of both observational and experimental research in adults aged 18–80 y that assessed depression scores in relation to polyphenol intake. A total of 37 studies out of 12,084 met the full inclusion criteria. Of these, 17 were experimental studies and 20 were observational studies. Several different polyphenols were assessed including those from tea, coffee, citrus, nuts, soy, grapes, legumes, and spices. Twenty-nine of the studies found a statistically significant effect of polyphenols for depression. This review has found both an association between polyphenol consumption and depression risk, as well as evidence suggesting polyphenols can effectively alleviate depressive symptoms. The review uncovered gaps in the literature regarding the role of polyphenols for depressive symptoms in both young adults and men. This review was registered at www.crd.york.ac.uk/PROSPERO as CRD42019125747. *Adv Nutr* 2020;11:602–615.

Keywords: polyphenols, phytochemicals, flavonoids, depression, major depressive disorder, mental health

Introduction

Depression is a mood disorder characterized by anhedonia or lack of pleasure, a depressed mood, and altered cognitive function (1). Currently, 350 million individuals suffer from depression globally (2), with the WHO estimating that mental health conditions are now the leading cause of disability worldwide (3). Although the exact etiology of depression is still unknown, several similarities exist between depression and inflammatory diseases such as cardiovascular disease, diabetes, and cancer which include reduced insulin sensitivity, endothelial dysfunction, and increased production of proinflammatory cytokines (4).

Supported by an Australian Government Research Training Program Scholarship (to JB).
Author disclosures: The authors report no conflicts of interest.
Supplemental Figure 1 and Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: CESD, Center for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; RCT, randomized controlled trial; ZSDS, Zung Self-Rating Depression Scale.

The field of nutritional psychiatry is relatively new and relates to the emerging research focusing on the role of diet and nutrition on mental health (5). New investigations into the microbiome, immune, and inflammation pathways demonstrate a powerful paradigm shift in the way we understand depression (6). Research into how diet and nutrition affects these pathways could yield valuable insights into potential treatment strategies for depression. A recent review examining the role of fruit and vegetable consumption and various health outcomes suggested several possible links between these foods and depression pathophysiology (7). The free-radical scavenging and anti-inflammatory components found in fruits and vegetables, particularly the high content of carotenoids, vitamin C, and polyphenols, appear to play an important role (7). Other possible therapeutic components include folate and the effects on methylation, homocysteine, and vitamin B-12 as well as the effect of fiber on gastric emptying and brain-derived neurotrophic factor (7).

Several traditional diets which are high in fruits and vegetables have been associated with a reduced risk of depression, including the traditional Japanese diet (8) and Norwegian diet (9). Currently, the diet with the most evidence for protecting against depression risk is the Mediterranean diet, which has recently been hypothesized as a promising treatment strategy for improving clinical outcomes in depression (10). Several reviews on diet and depression have speculated that the efficacy of the Mediterranean diet for depression may be due to the high polyphenol content (10–12). Therefore, conducting a systematic review to examine the research on these polyphenols may assist in verifying this potential mechanism of action.

The term "Mediterranean diet" reflects the diets of several countries in the Mediterranean Basin during the early 1960s (13). It was noted that the populations within these countries had reduced mortality and morbidity from various diseases (14). One of the common linking factors was their shared dietary pattern which has since gained much attention, particularly for preventing coronary artery disease (15). In 1993 the International Conference on the Diets of the Mediterranean defined the various components of the diet (13), concluding that it is abundant in plant foods such as fruits, vegetables, whole grains, nuts, seeds, and legumes. The principal source of dietary lipids is in the form of olive oil. Red wine is consumed in moderate amounts generally with meals (13). All of these dietary components are rich in polyphenols which may explain the favorable health outcomes, particularly in depression.

Polyphenols are natural compounds found in a wide variety of foods and are particularly high in plant-based foods (16). Polyphenols exert protective effects on mental health via upregulating the body's natural defense systems, stabilizing free radicals, and reducing oxidative damage (17). In addition, neuroprotective properties have been observed, with polyphenols modulating specific cellular signaling pathways involved in cognitive processes (17). The main classes of polyphenols are defined according to the nature of their carbon skeleton: phenolic acids, flavonoids, and the less common stilbenes and lignans (18).

The aim of this literature review is to assess the effects of polyphenols on the symptoms of depression.

Methods

A protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 statement (19). This review is registered with PROSPERO (CRD42019125747).

Search strategies and inclusion criteria

A literature search was conducted in the following databases: PROQUEST, SCOPUS (Elsevier), MEDLINE (EBSCO), CINAHL, and EMBase. Search terms were divided into 2 groups and combined within the search as follows: group 1: polyphenols OR phytochemicals OR flavonoids; group 2: depression OR major depressive disorder OR major depression OR mental health. Initial investigations on search terms for group 1 included the search terms phenolic acids, ligands, stilbenes, and anthocyanins. These terms found no results and hence were excluded from the group.

Original research, published up to 18 February, 2019, which assessed the effect of polyphenols on the symptoms of depression was included in the review. All fruits, vegetables, nuts and seeds, wholegrains, beans and legumes, plant oils, and common culinary herbs and spices were included. As far as we know, this is the first literature review to assess the role of polyphenols on depressive symptoms.

Articles were excluded from the review for the following reasons: not published in English; not related to the search terms such as those articles on Alzheimer disease or cognitive decline; not original research; did not use a depression rating scale; or examined polyphenols not usually consumed as part of the diet such as the medicinal herbs St. John's wort, lavender, and Ginkgo biloba.

Study selection and data extraction

The initial search identified 12,084 articles. After removal of 790 duplicates, articles were screened by title and by abstract. The remaining articles were then screened by full text, resulting in 35 articles which met the full inclusion criteria. After hand-searching the references of the full-text articles an additional 2 articles which used different keywords were included. This resulted in 37 articles to be assessed in this review. Screening was performed by JB and citations were stored and filed in EndNote X7. The article selection process is outlined in **Supplemental Figure 1**.

Assessment of risk of bias and data summary tables

Each article was critically appraised for methodological consistency using critical appraisal tools. For the 17 experimental studies the Joanna Briggs Institute critical appraisal tool for systematic reviews Checklist for Randomized Controlled Trials was used (20). For the 20 observational studies the STROBE checklist for cohort, case-control, and cross-sectional studies was used (21). Overall, the appraisals found reliable methodology and no articles were excluded from the review. **Supplemental Table 1** displays the results for the randomized controlled trials (RCTs) and **Supplemental Table 2** displays the results for the observational studies. During this process data were extracted from the final articles and summarized in **Tables 1** and **2**.

Results

Study characteristics

All included studies provided quantitative data on human subjects. The observational studies included both longitudinal cohort and cross-sectional designs and had a mean number of 10,301 participants. The experimental studies were RCTs with either a placebo or an antidepressant medication with an average number of 80 participants. The experimental studies varied in time duration from 2 wk to 2 y with the most common time frame being 8 wk. The

TABLE 1 Data summary of experimental trials assessing polyphenols in depressed participants[1]

Author	Year	Country	Study design	Intervention	Subjects	Depression scale	Other measurements	Results
Sathyapalan et al. (22)	2010	England	Randomized placebo-controlled trial. Duration: 8 wk of the initial intervention followed by a 2-wk washout period followed by 8 wk of the crossover intervention.	1: Polyphenol-rich chocolate with 85% cocoa solids. 2: Placebo chocolate.	10 subjects ($n = 6$ women; $n = 4$ men). Condition: chronic fatigue.	HADS	Chalder fatigue scale and London handicap scale	Depression scores improved after the high-polyphenol chocolate but deteriorated after the placebo chocolate. Cocoa group HADS median scores: baseline = 10, conclusion = 5.5. Placebo: baseline = 6, conclusion = 12. However, the results were nonsignificant: Wilcoxon's signed rank sum test Z value: −2.68 (SD: 0.01).
Bergman et al. (23)	2013	Israel	Randomized, double-blinded, placebo-controlled, pilot clinical trial. Duration: 5 wk.	1: 500 mg curcumin/d plus antidepressant. 2: Placebo plus antidepressant.	40 subjects ($n = 23$ women; $n = 17$ men)	HAM-D and MADRS	Global Impression Severity Scale	Both groups had a significant improvement in depressive symptoms. MADRS score for the curcumin group 95% CI: 7.2, 13.7; $P \leq 0.001$ and placebo group 95% CI: 2.1, 8.5; $P \leq 0.01$. Although no significant differences were observed between the intervention and placebo, the curcumin group displayed a more rapid improvement in symptoms than the placebo. Curcumin group MADRS mean scores: baseline = 34.4, conclusion = 14.0. Placebo: baseline = 32.8, conclusion = 15.4.
Nina Estrella et al. (24)	2014	Dominican Republic	Pilot randomized clinical study. Duration: 3-mo with 4 intervention arms.	1: 10 mg fluoxetine /d. 2: 100 mg soy isoflavones concentrate/d. 3: 50 mg sertraline/d. 4: 100 mg soy/d and 50 mg sertraline/d.	40 women aged 45–55 y. Condition: menopausal depressive.	ZSDS. HAM-D	Not reported	ANOVA for both ZSDS and HAM-D showed statistically significant differences between groups ($F = 24.06$, $P \leq 0.0001$ and ($F = 31.73$, $P \leq 0.0001$, respectively). Soybean has an antidepressant effect and may increase the effects of antidepressants.
Atteritano et al. (25)	2014	Italy	Double-blinded RCT. Duration: 2 y.	1: Isoflavone genistein (45 mg/d). 2: Placebo.	262 women. Condition: osteopenic postmenopausal.	ZSDS	HRQL assessed via Italian version of Short Form-36	The genistein group saw a decrease in depression scores after 1 and 2 y. The difference between groups was statistically significant ($P \leq 0.01$ vs. placebo). Genistein group ZSDS mean scores: baseline = 41, conclusion = 36. Placebo: baseline = 41, conclusion = 43.
Lopresti et al. (26)	2014	Australia	Randomized double-blinded, placebo-controlled trial. Duration: 8 wk.	1: 500 mg curcumin twice daily. 2: Placebo.	56 subjects ($n = 40$ women; $n = 16$ men)	IDS-SR 30	Spielberger State-Trait Anxiety Inventory	From week 4 to week 8 the curcumin group demonstrated significantly more efficacy than placebo. IDS-SR total score: $F_{1,53} = 4.22$, $P = 0.045$; and mood score: $F_{1,53} = 6.51$, $P = 0.014$. Curcumin group IDS-SR total mean scores: baseline = 33, conclusion = 22.7. Placebo: baseline = 33, conclusion = 25.8.
Sanmukhani et al. (27)	2014	India	Double-blinded RCT. Duration: 6 wk.	1: 20 mg fluoxetine/d. 2: 1000 mg curcumin/d (500 mg twice daily). 3: 20 mg fluoxetine/d plus 1000 mg curcumin/d (500 mg twice daily).	40 subjects ($n = 24$ women; $n = 16$ men)	HAM-D_{17}	Clinical Global Impression—severity of illness scale	A greater response was observed in the combined fluoxetine and curcumin group (77.8%) than in the fluoxetine group (64.7%) and the curcumin group (62.5%). However, the differences between groups were statistically nonsignificant ($P = 0.58$). Group 1 HAM-D mean scores: baseline = 21, change from baseline at conclusion = −13.6. Group 2 baseline = 19.3, change at conclusion = −13.3. Group 3 baseline = 21.9, change at conclusion = −14.6.

(*Continued*)

TABLE 1 (*Continued*)

Author	Year	Country	Study design	Intervention	Subjects	Depression scale	Other measurements	Results
Esmaily et al. (28)	2015	Iran	Double-blind, crossover, placebo-controlled RCT. Duration: 4 wk with a 2-wk washout between groups.	1: 1 g curcumin/d. 2: Placebo.	30 subjects ($n = 24$ women; $n = 6$ men). Condition: obese.	BDI	Beck Anxiety Inventory	No significant differences in BDI scores were observed for the curcumin group ($P \geq 0.05$).
Panahi et al. (29)	2015	Iran	Open-label RCT. Duration: 6 wk.	1: Standard antidepressant therapy. 2: Standard antidepressant therapy plus 1000 mg curcuminoids/d and 10 mg piperine/d.	111 subjects ($n = 60$ women; $n = 51$ men)	HADS and BDI	Not reported	Significantly reduced HADS and BDI scores in the curcumin group compared with the control group. HADS score, $P \leq 0.001$; BDI score, $P \leq 0.001$. Curcuminoids group BDI mean scores: baseline = 38.66, conclusion = 29.66. Placebo: baseline = 40.44, conclusion = 37.60. Curcuminoids group HADS mean scores: baseline = 42.59, conclusion = 30.90. Placebo: baseline = 38.82, conclusion = 36.10.
Yu et al. (30)	2015	China	Double-blinded, placebo-controlled, pilot RCT. Duration: 6 wk.	1: 1000 mg curcumin/d. 2: Placebo soybean powder.	108 male subjects	Chinese version of the 17-item HAM-D and MADRS	Blood pathology: plasma cytokines IL-1β, TNF-α, and BDNF	Significant reduction in depressive symptoms in the curcumin group for both the HAM-D and MADRS ($P \leq 0.05$). Significant reduction in cytokines IL-1β, TNF-α, and BDNF for the curcumin group ($P \leq 0.001$). Curcumin group HAM-D mean scores: baseline = 14.06, change from baseline at conclusion = 4.52. Placebo: baseline = 14.28, change from baseline at conclusion = 3.30. Curcumin group MADRS mean scores: baseline = 18.22, change from baseline at conclusion = 6.26. Placebo: baseline = 18.68, change from baseline at conclusion = 4.52.
Ibero-Baraibar et al. (31)	2016	Spain	Double-blinded, randomized, placebo-controlled trial. Duration: 4 wk.	1: 15% energy-restriction diet plus 1.4 g cocoa extract twice daily (645 mg total polyphenols). 2: 15% energy-restriction diet only.	50 subjects ($n = 27$ women; $n = 23$ men). Condition: overweight or obese adults.	Spanish translation of the BDI	3-d food recall questionnaire	Depressive symptoms were reduced significantly in both experimental groups ($P \leq 0.05$). However, no differences were observed in depression scores between the 2 groups. Cocoa group BDI mean scores: baseline = 9.4, conclusion = 5.7. Placebo: baseline = 11.8, conclusion = 6.1.
Pribis (32)	2016	United States	Double-blinded, randomized, placebo-controlled, crossover design. Duration: 8-wk intervention followed by 6-wk washout period followed by 8-wk crossover intervention.	1: Banana bread with 60 g ground walnuts. 2: Banana bread without walnuts.	49 subjects ($n = 29$ women; $n = 20$ men). Condition: students aged between 18 and 25 y.	The Profile of Mood States	Lifestyle survey and FFQ	Men, but not women, had a significant medium-effect-size improvement in total mood disturbances. Both men and women had a nonstatistically significant improvement in depression ($P = 0.103$).
Hirose et al. (33)	2016	Japan	Randomized, double-blinded, placebo-controlled trial. Duration: 8 wk.	1: 12.5 mg isoflavone aglycone/d. 2: 25 mg isoflavone aglycone/d. 3: Placebo.	90 women aged 40–60 y. Condition: menopausal.	HADS	Menopausal symptom scale and Athens Insomnia Scale	Low-dose (25 mg/d) isoflavone aglycone significantly reduced symptoms of depression ($P = 0.033$).

(*Continued*)

TABLE 1 (*Continued*)

Author	Year	Country	Study design	Intervention	Subjects	Depression scale	Other measurements	Results
Mirghafourvand et al. (34)	2017	Iran	RCT. Duration: 8 wk.	1: Orange peel essential oil (10 drops 3 times/d). 2: Placebo.	48 women. Condition: postpartum.	The Edinburgh Postnatal Depression Questionnaire	The Spielberger State-Trait Anxiety Inventory	No statistically significant difference between intervention and placebo ($P = 0.956$). Orange peel group depression mean scores: baseline = 8.0, conclusion = 6.7. Placebo: baseline = 8.1, conclusion = 6.7.
Kamalifard et al. (35)	2017	Iran	Triple-blind RCT. Duration: 8 wk.	1: 500 mg bitter orange powder/d. 2: 500 mg lavender flower powder/d. 3: 500 mg placebo (starch)/d.	156 women aged 45–60 y. Condition: menopausal.	BDI	Sociodemographic questionnaire	Both orange and lavender were effective at reducing symptoms of depression compared with placebo ($P = 0.001$). There was no significant difference between orange and lavender. Bitter orange group BDI mean scores: baseline = 21.38, conclusion = 14.48. Lavender: baseline = 20.82, conclusion = 14.07. Placebo: baseline = 20.01, conclusion = 16.78.
Davinelli et al. (36)	2017	Italy	Randomized, double-blinded, placebo-controlled trial. Duration: 12 wk.	1: Capsule containing 200 mg fermented soy (80 mg isoflavone aglycones and 10 mg equol) and 25 mg resveratrol/d. 2: Placebo capsule.	60 women aged 50–55 y. Condition: menopausal.	HAM-D	HRQL Menopause Rating Scale	Treatment group saw improvements in depression scores in comparison with the placebo group ($P = 0.001$).
Kazemian et al. (37)	2017	Iran	RCT. Duration: 1 mo.	1: Capsule containing *Zingiber officinale* (ginger), *Boswellia carterii* (frankincense), and *Achillea millefolium* (yarrow) daily. 2: Placebo.	42 subjects ($n = 19$ women; $n = 23$ men). Condition: IBS.	HADS	IBS-SSS	Symptoms of depression reduced significantly in the intervention group ($P = 0.001$) with no significant changes in the placebo group ($P = 0.31$). Herb group HADS mean scores: baseline = 17.4, conclusion = 12.5. Placebo: baseline = 18.0, conclusion = 17.22.
Chang and Chen (38)	2018	Taiwan	Single-blinded, placebo-controlled, randomized clinical trial. Duration: 2 wk.	1: Chamomile tea (1 cup/d which included 2 g dried flowers and 300 mL hot water steeped for 10–15 min). 2: Regular care with no chamomile tea.	80 women. Condition: 6 wk postpartum.	Edinburgh Postnatal Depression Scale	Postpartum Fatigue Scale	The chamomile tea group significantly lowered depressive symptoms compared with the control group ($T = -2.372$, $P = 0.020$). Chamomile group depression mean scores: baseline = 7.86, conclusion = 7.26. Placebo: baseline = 9.71, conclusion = 9.51.

[1] BDI, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; HRQL, health-related quality of life; IBS, irritable bowel syndrome; IBS-SSS, irritable bowel syndrome-severity scoring system; IDS-SR, Inventory of Depressive Symptomatology self-rated scale; MADRS, Montgomery-Asberg Depression Rating Scale; RCT, randomized controlled trial; ZSDS, Zung Self-Rating Depression Scale.

TABLE 2 Data summary of observational studies assessing the effects of polyphenols on depressive symptoms[1]

Author	Year	Country	Study design	Main variable	Subjects	Depression scale	Other measures	Results
Hintikka et al. (39)	2005	Finland	Cross-sectional study	Tea consumption	2011 participants from the Kuopio Depression Study aged 25–64 y ($n = 1121$ women; $n = 890$ men)	Beck Depression Inventory	FFQ	Daily tea drinkers had a significantly reduced risk of being depressed (OR: 0.46, 95% CI: 0.3, 0.7).
Niu et al. (40)	2009	Japan	Cross-sectional study	Green tea consumption	1058 elderly participants >70 y old	30-item GDS	Height and weight, blood tests for C-reactive protein. A 75-item diet history questionnaire.	The prevalence of depressive symptoms was 44% lower for participants who consumed ≥4 cups of green tea than for those who consumed ≤1 cup/d (Bonferroni-corrected $P \leq 0.01$).
Chen et al. (41)	2010	China	Prospective cohort study	Tea consumption	1399 women. Condition: breast cancer survivors.	20-item CESD	Quality of Life and Medical Outcomes Short-Form 36 Health Survey	Regular tea consumption (>100 g dried tea leaves/mo) was inversely associated with overall depression (OR: 0.64; 95% CI: 0.41, 0.99).
Ruusunen et al. (42)	2010	Finland	Prospective cohort study	Coffee and tea consumption	2232 middle-aged men	18-item Human Population Laboratory Depression Scale	4-d food record, BMI	Heavy coffee drinkers had a decreased risk of depression compared with nondrinkers (RR: 0.28; 95% CI: 0.08, 0.98). No associations were observed for tea consumption and depression (RR: 1.19; 95% CI: 0.54, 2.23).
Li et al. (43)	2010	United States	Longitudinal cohort study. Duration: cohort from 1971 to 1982.	Legume consumption	4869 adults who participated in the NHANES (NHANES I)	CESD	3-mo FFQ	In premenopausal women, consumption of legumes was associated with an increased risk of depression ($P = 0.0148$). However, moderate consumption was associated with a lower risk of depression among perimenopausal women (RR: 0.52; 95% CI: 0.27, 1.00). No significant association was found among men or postmenopausal women.
Lucas et al. (44)	2011	United States	Prospective longitudinal study. Duration: 10-y follow-up.	Coffee consumption	50,739 women (mean age 63 y)	36-item short-form health survey	FFQ	Depression risk decreases with increasing coffee intake. Multivariate RR for those consuming ≥4 cups/d was 0.80 (95% CI: 0.68, 0.95; P for trend = 0.02).
Feng et al. (45)	2012	Singapore	Prospective cohort study	Tea consumption	1615 older participants aged 55–93 y	15-item GDS	FFQ	Risk of depression decreased with increasing tea consumption. OR for low, medium, and high tea consumption was 1.15, 0.55, and 0.37, respectively (P for linear trend = 0.01).
Feng et al. (46)	2013	China	Cross-sectional study	Tea consumption	1368 older-aged participants ≥60 y	15-item GDS	Mini Mental State Examination. Tea consumption questionnaire	Daily tea consumption was associated with a reduced risk of depressive symptoms. Weekly tea consumption OR: 0.86 (95% CI: 0.56, 1.32) and daily consumption OR: 0.59 (95% CI: 0.43, 0.81) (P for linear trend = 0.001).
Omagari et al. (47)	2014	Japan	Cross-sectional study	Coffee consumption	89 participants with type 2 diabetes ($n = 34$ women; $n = 55$ men)	Japanese version of the Hospital Anxiety and Depression Scale	FFQ and BMI	Coffee consumption was inversely associated with depressive symptoms, with participants who drank ≥3 cups/d having a significantly reduced risk of depression ($P = 0.032$).
Pham et al. (48)	2014	Japan	Cross-sectional study	Green tea and coffee consumption	537 men	CESD	Diet history questionnaire, C-reactive protein and folate blood test.	Higher green tea consumption (≥4 cups/d) was associated with a significantly lower prevalence of depressive symptoms (51% lower prevalence odds) (P for trend = 0.01). Coffee consumption was also inversely associated with depressive symptoms, with ≥2 cups/d compared with 1 cup/d OR: 0.61 (95% CI: 0.38, 0.98).
Yu et al. (49)	2015	China	Cross-sectional study	Soybean and soybean product consumption	1717 Liaoning Province residents aged >65 y ($n = 849$ women; $n = 868$ men)	PHQ-9	FFQ	Frequent consumption of soybeans and soybean products was associated with a decrease in the likelihood of depressive symptoms. Consumption 2–3 times/wk OR: 0.36 (95% CI: 0.15, 0.87; $P = 0.23$). Consumption >4 times/wk OR: 0.50 (95% CI: 0.34, 0.74; $P = 0.001$).

(*Continued*)

TABLE 2 (*Continued*)

Author	Year	Country	Study design	Main variable	Subjects	Depression scale	Other measures	Results
Li et al. (50)	2016	China	Cross-sectional study	Tea consumption	9371 elderly (≥60 y of age) participants ($n = 4853$ women; $n = 4518$ men)	PHQ-9	Daily living scale and the Mini Mental State Examination. FFQ	Black tea drinkers had a significantly decreased risk of depressive symptoms ($P \leq 0.01$) compared with nondrinkers (adjusted OR: 0.48; 95% CI: 0.23, 0.99 and OR: 0.35; 95% CI: 0.17, 0.72 for participants consuming <3 cups and ≥3 cups of black tea per day, respectively) (P for trend < 0.01).
Chang et al. (51)	2016	United States	Longitudinal cohort study. Duration: 1976–2001	Dietary flavonoid intake	82,648 women who participated in the Nurses' Health Study	The 5-item mental health index, the CESD-10, and the GDS	FFQ	Greater intakes of dietary flavonoids were significantly associated with a modest reduction in depression risk. Participants in the highest flavonoid consumption group had a 7–10% reduction in depression risk compared with the lowest intake group. There was evidence of an inverse linear trend across consumption groups (P-trend = 0.08, 0.0004, and 0.0007, respectively).
Su et al. (52)	2016	China	Cross-sectional study	Nut consumption	13,626 adults who participated in the Tianjin Chronic Low-Grade Systemic Inflammation and Health Cohort. Recruited during 2013–2014.	ZSDS	FFQ	Frequent nut consumption is associated with lower prevalence of depression (OR: 0.82; 95% CI: 0.75, 0.90 for consumption 1–3 times/wk and OR: 0.82; 95% CI: 0.73, 0.92 for consumption ≥4 times/wk).
Chan et al. (53)	2018	Singapore	Prospective cohort study	Tea consumption	614 elderly participants aged ≥60 y	15-item GDS	Geriatric Anxiety Scale. Tea consumption questionnaire.	Long-term tea consumption was significantly associated with reduced odds of depressive symptoms. Tea consumption for >15 y resulted in lower GDS scores (OR: 0.82; $P = 0.01$).
Navarro et al. (54)	2018	Spain	Longitudinal cohort study	Coffee consumption	14,413 middle-aged participants	Validated physician diagnosis of depression using the Structured Clinical Interview for DSM-IV	FFQ	Greater coffee consumption is associated with reduced risk of depression. Participants who drank ≥4 cups/d showed a significantly lower risk of depression than participants who drank <1 cup of coffee per day (HR: 0.37; 95% CI: 0.15, 0.95).
Miyake et al. (55)	2018	Japan	Cross-sectional study	Soy isoflavones	1745 pregnant women who participated in the Kyushu Okinawa Maternal and Child Health Study (an ongoing prospective prebirth cohort study)	CESD	Diet history questionnaire	Isoflavone intake was associated with a lower prevalence of depressive symptoms during pregnancy. Prevalence ratios (95% CIs; P for trend): 0.63 (0.47, 0.85; 0.002), 0.72 (0.54, 0.96; 0.007), 0.74 (0.56, 0.98; 0.04), 0.57 (0.42, 0.76; <0.0001), 0.73 (0.55, 0.98; 0.03), 0.65 (0.49, 0.87; 0.003), and 0.63 (0.46, 0.86; 0.002).
Yu et al. (56)	2018	China	Cross-sectional study	Soy isoflavones	13,760 adults who participated in the Tianjin Chronic Low-Grade Systemic Inflammation and Health Cohort	ZSDS	FFQ	Moderate intake of soy foods may reduce the incidence of depression, whereas high intakes may worsen depressive symptoms. OR: 95% CI (vs. <1/wk) were 0.80 (0.67, 0.95) for 1–3/wk, 0.69 (0.55, 0.86) for 4–7/wk, and 1.85 (1.21, 2.80) for ≥2/d.
Godos et al. (57)	2018	Italy	Cross-sectional study	Dietary polyphenols	1572 adults who participated in the Mediterranean Healthy Eating, Lifestyle and Aging study	CESD	FFQ	Higher dietary flavonoid intake may be inversely associated with depressive symptoms (P for trend < 0.001). Dietary intake of phenolic acid (OR: 0.64; 95% CI: 0.44, 0.93), flavanones (OR: 0.54; 95% CI: 0.32, 0.91), and anthocyanins (OR: 0.61; 95% CI: 0.42, 0.89) showed significant inverse association with depressive symptoms, when comparing the highest with the lowest quartile.
Mofrad et al. (58)	2019	Iran	Cross-sectional study	Dietary phytochemicals	488 women aged 20–50 y	Depression, anxiety, stress scale	FFQ	Higher consumption of dietary phytochemicals is associated with a decrease in depressive symptoms (OR: 0.22; 95% CI: 0.12, 0.38; $P \leq 0.001$).

[1] CESD, Center for Epidemiologic Studies Depression Scale; GDS, Geriatric Depression Scale; PHQ, Patient Health Questionnaire; ZSDS, Zung Self-Rating Depression Scale.

majority of the studies assessed both genders ($n = 23$), 12 assessed only females, and only 2 studies assessed only men. Twenty-six of the studies were in adults aged between 23 and 55 y; 10 were in older adults, either postmenopausal or the elderly aged between 40 and 80 y; and only 1 study was in young adults aged 18–25 y. Twelve studies looked at depression in disease states. These included major depressive disorder (23, 26, 27, 29, 30), chronic fatigue syndrome (22), osteopenia (25), obesity (28, 31), breast cancer (41), type 2 diabetes (47), and irritable bowel syndrome (37). An overview of these study characteristics can be viewed in **Table 3**.

Critical appraisal

Overall, the results from the critical appraisal tools showed good methodology. Results can be seen in Supplemental Tables 1 and 2. A common weakness observed in the experimental studies was the lack of information in regards to blinding. Although the majority of studies claimed to be double blinded in either the title or the abstract, many failed to provide details of how the assessors and those delivering the interventions were blinded in the methodology section. In the observational studies, common weaknesses included failure to explain how loss of follow-up was addressed, not describing study design bias, not providing a flow diagram to show included participants, and failing to indicate the number of participants with missing data for each variable of interest. These limitations were considered when synthesizing the results from this review.

Depression scales

The most common depression scale used in the observational studies was the Center for Epidemiologic Studies Depression Scale (CESD), which was used in 6 of the 20 studies (41, 43, 48, 51, 55, 57). The CESD is a 20-item measure that asks subjects to rate how often over the past week they experienced symptoms associated with depression, such as restless sleep, poor appetite, and feeling lonely (59). In the experimental studies the most common scale used was the Hamilton Rating Scale for Depression, which was used in 5 of the 17 studies (23, 24, 27, 30, 36). The second most popular scale was the Hospital Anxiety and Depression Scale (HADS), which was used in 4 of the studies (22, 29, 33, 37). The HADS is a 14-item scale used to measure anxiety and depression in a hospital or community setting (60). Another popular depression scale used was the Zung Self-Rating Depression Scale (ZSDS), which was used in both observational (52, 56) and experimental designs (24, 25). The ZSDS is a 20-item self-report questionnaire covering affective, psychological, and somatic symptoms associated with depression (61).

Polyphenols

A variety of different polyphenols were assessed in the articles included in this review. The observational studies looked at polyphenols consumed in their biological whole food form and the majority of experimental studies assessed the effect of polyphenols consumed via a capsule (23–31, 33, 36, 37), powder (35), dried herbal tea (38), or liquid (34). Only 2 experimental studies assessed polyphenols consumed in their whole food form (22, 32). The most commonly tested groups of polyphenols were flavanols from tea ($n = 9$ observational) and cocoa ($n = 2$ experimental), isoflavones from soy ($n = 3$ observational and $n = 4$ experimental), and hydroxycinnamic acids from coffee ($n = 5$ observational) and curcumin ($n = 6$ experimental). Other classes of polyphenols tested included flavanones in the form of citrus ($n = 2$ experimental), stilbenes in the form of resveratrol ($n = 1$ experimental), and flavonols in the form of nuts ($n = 1$ observational and $n = 1$ experimental). Three of the observational studies considered the combined effect of all dietary sources of polyphenols in depression risk (51, 57, 58).

Intervention/variable effect

The majority of studies ($n = 29$) found a statistically significant positive and protective effect of consuming polyphenols on the symptoms and risk of depression. Five studies noted a positive effect which was not statistically significant (22, 23, 27, 32, 52), 2 studies reported mixed results (43, 56), and only 2 studies showed no difference after the intervention (28, 34). An overview of the effect of polyphenols on depression is displayed in **Table 4**. *P* values are given for experimental studies in Table 1 and ORs, RRs, and *P* values are given for observational studies in Table 2.

Discussion

This systematic review provides important insights into the role polyphenols play in depression. The cross-sectional and cohort studies reported on represent the polyphenol intake of individuals in a real-life setting and estimate the prevalence of depression among low, moderate, and high consumers of polyphenols. The majority ($n = 17$) of these studies found a statistically significant result (39–42, 44–51, 53–55, 57, 58) suggesting that a higher polyphenol intake is associated with decreased prevalence of depression. Polyphenol intake was measured via various different FFQs and diet history forms. Several challenges exist with these methods such as under- or over-reporting consumption and measurement error (62) and these factors must be considered when interpreting the results. However, the results from these observational studies provide a strong foundation for suggesting that polyphenols play a role in depression, but they can only infer correlation in regards to disease risk and prevalence.

The 17 experimental trials included in this systematic review can provide more information about causation in regards to polyphenols exerting a therapeutic benefit for depressive symptoms. These experimental results demonstrate a positive therapeutic benefit for depression with various different polyphenols appearing to reduce depressive symptoms. In contrast to the observational studies which looked at depression risk in healthy individuals, the experimental studies assessed individuals presenting with

TABLE 3 Characteristics of included articles[1]

Authors	Sex			Age					Disease	Polyphenols									
Experimental	M	F	B	Young adult	Adult	Pregnancy or postpartum	Menopause	Postmenopausal or elderly	Disease state	Soy	Citrus	Resveratrol	Cocoa	Nut	Legume	Herb and spice	Coffee	Tea	All polyphenols
Sathyapalan et al. (22)			X						X				X						
Bergman et al. (23)			X		X				X							X			
Nina Estrella et al. (24)		X			X		X			X									
Atteritano et al. (25)		X						X	X	X									
Lopresti et al. (26)			X		X				X							X			
Sanmukhani et al. (27)			X		X				X							X			
Esmaily et al. (28)			X		X				X							X			
Panahi et al. (29)			X		X				X							X			
Yu et al. (30)	X				X				X							X			
Ibero-Baraibar et al. (31)			X		X				X				X						
Pribis (32)			X	X										X					
Hirose et al. (33)		X			X		X			X									
Mirghafourvand et al. (34)		X			X	X					X								
Kamalifard et al. (35)		X			X		X				X								
Davinelli et al. (36)		X			X		X			X		X							
Kazemian et al. (37)			X		X				X							X			
Chang and Chen (38)		X				X										X			
Hintikka et al. (39)			X		X													X	
Niu et al. (40)			X					X										X	
Chen et al. (41)		X			X				X									X	
Ruusunen et al. (42)	X				X												X	X	
Li et al. (43)			X		X			X							X				
Lucas et al. (44)		X						X									X		
Feng et al. (45)			X					X										X	
Feng et al. (46)			X					X										X	
Omagari et al. (47)			X		X				X								X		
Pham et al. (48)			X		X												X	X	
Yu et al. (49)			X					X		X									
Li et al. (50)			X					X										X	
Chang et al. (51)		X			X			X											X
Su et al. (52)			X		X									X					
Chan et al. (53)			X					X										X	
Navarro et al. (54)			X		X												X		
Miyake et al. (55)		X			X	X				X									
Yu et al. (56)			X		X					X									
Godos et al. (57)			X		X														X
Mofrad et al. (58)		X			X														X

[1] B, both genders; F, female; M, male.

TABLE 4 Effect of polyphenols on symptoms of depression[1]

Authors	Positive effect: statistically significant	Positive effect: not statistically significant	Mixed results	No difference observed
Experimental				
Sathyapalan et al. (22)		X		
Bergman et al. (23)		X		
Nina Estrella et al. (24)	X			
Atteritano et al. (25)	X			
Lopresti et al. (26)	X			
Sanmukhani et al. (27)		X		
Esmaily et al. (28)				X
Panahi et al. (29)	X			
Yu et al. (30)	X			
Ibero-Baraibar et al. (31)	X			
Pribis (32)	X*	X		
Hirose et al. (33)	X			
Mirghafourvand et al. (34)				X
Kamalifard et al. (35)	X			
Davinelli et al. (36)	X			
Kazemian et al. (37)	X			
Chang and Chen (38)	X			
Observational				
Hintikka et al. (39)	X			
Niu et al. (40)	X			
Chen et al. (41)	X			
Ruusunen et al. (42)	X			
Li et al. (43)			X	
Lucas et al. (44)	X			
Feng et al. (45)	X			
Feng et al. (46)	X			
Omagari et al. (47)	X			
Pham et al. (48)	X			
Yu et al. (49)	X			
Li et al. (50)	X			
Chang et al. (51)	X			
Su et al. (52)		X		
Chan et al. (53)	X			
Navarro et al. (54)	X			
Miyake et al. (55)	X			
Yu et al. (56)			X	
Godos et al. (57)	X			
Mofrad et al. (58)	X			

[1] X, study contains this item.
*Only significant in males.

depressive symptoms or who were diagnosed with depression before the commencement of the intervention. The majority ($n = 9$) looked at depressive symptoms (22, 25, 28, 31–34, 37, 38), with 8 of the studies assessing participants with diagnosed clinical depression (23, 24, 26, 27, 29, 30, 35, 36). Of these studies, several also included antidepressant use either as the active control or in combination with a polyphenol. These included escitalopram (23, 30), venlafaxine (23), fluoxetine (24, 27), and sertraline (24). The studies which used polyphenols in combination with antidepressants found that the antidepressive effects of the polyphenol/antidepressant combination were greater than those of the antidepressant as a monotherapy (23, 24, 27, 30). Further investigations into the effects of polyphenols in individuals with clinical depression are needed and should be the focus of future studies in this area.

The findings of this systematic review of polyphenols are in part supported by a recent meta-analysis which highlighted the protective role of adhering to a Mediterranean diet for depression risk (63). The authors suggested that the protective role of the Mediterranean diet could be multidimensional, encompassing both anti-inflammatory functions and protection from oxidative stress (63, 64). Depression is commonly associated with a subclinical inflammatory status characterized by an increase in proinflammatory cytokines and neuronal damage (57), which could be the pathways targeted by this dietary pattern.

The polyphenols that this review has highlighted as being effective include soy isoflavones (24, 25, 33, 49, 55, 56), tea (39–41, 45, 46, 48, 50, 53) and cocoa flavanols (22, 31), curcumin (26, 29, 30) and coffee hydroxycinnamic acid (42, 44, 47, 48, 54), walnut flavonols (32, 52), citrus flavanones

(35), and the stilbene resveratrol (36). Polyphenols are naturally produced plant compounds which form part of the plants' defense mechanisms protecting them from pathogens and ultraviolet radiation (17). Several animal studies have demonstrated that polyphenols reduce depression-like behavior in rodents (16). Studies have suggested an interaction between polyphenols and monoamine oxidase, an enzyme utilized in the catabolism of monoamines, thus reducing the breakdown of monoaminergic neurotransmitters and increasing serotonin and dopamine concentrations (17). Another possible mechanism for how polyphenols exert their beneficial effects on mental health includes their anti-inflammatory properties via inhibition of proinflammatory cytokines, free radical scavenging, and antioxidant activity as well as neuroprotective properties (65).

However, the antioxidant activity, bioavailability, and enzyme and cell-receptor interactions vary greatly depending on the chemical structure of different polyphenols (18). The structure of polyphenols affects the rate and extent of intestinal absorption which, in turn, affects the metabolites circulating in the plasma (18). In addition, the polyphenols which are the most common in the diet may not necessarily be the most active due to poor intestinal absorption or high metabolism and excretion from the body (66). Studies suggest that the majority of polyphenols are not actually absorbed through the intestinal barrier, but are metabolized by colonic microflora farther down the digestive tract (18). Research even suggests that metabolism pathways and metabolites of polyphenols may be one of the characteristics responsible for their therapeutic effects (66). A review found that gallic acid and isoflavones have the best absorption rates, with proanthocyanins displaying the poorest absorption (67). The differences in bioavailability and absorption rates of various polyphenols are an important limitation of this review and should be considered when interpreting the results.

Several studies have demonstrated that the absorption rate of curcumin is relatively poor (68–70) and the inclusion of piperine in order to enhance absorption is often recommended (70). Of the 6 studies included in this review which tested curcumin, 3 included an absorption enhancer (23, 28, 29) and 3 did not (26, 27, 30), which may have affected the results. All 6 studies were randomized clinical trials, with 3 displaying statistically significant results (26, 29, 30). More studies on the therapeutic use of curcumin for depression are needed before firm conclusions can be drawn. Other promising polyphenols include those from tea and coffee. Tea and coffee are 2 of the most commonly consumed beverages worldwide (71) and act as a major source of total dietary polyphenol intake (18). All of the 12 studies on tea and coffee included in this review were observational studies. RCTs are needed to determine if a cause and effect relation also exists for these polyphenols.

A common theme present throughout several of the studies is the use of isoflavones for women, either during menopause or in postmenopausal and elderly women. Isoflavones are flavonoids abundant in legumes which are able to influence hormone concentrations by binding to some estrogen receptors and are thus referred to as phytoestrogens (33). It has been suggested that isoflavones may alleviate the symptoms of depression which commonly accompany menopause by modulating the dramatic fluctuations in ovarian hormones which occur during this period (55). This potential mechanism of action suggests that isoflavones may only be effective in this specific demographic.

This hypothesis is further supported by the study by Li et al. (43), which found mixed results when comparing the results between men, women, and menopausal status. The researchers found that in premenopausal women consumption of legumes was associated with an increased risk of depression. However, moderate consumption was associated with a lower risk of depression among perimenopausal women. No significant association was found among men or postmenopausal women (43). Together, these findings support the theory that isoflavones may exert their beneficial effect for depression by acting as phytoestrogens and therefore may only be appropriate for use in specific population groups.

This review has limitations of its own which need to be acknowledged. The initial search resulted in a large number of very diverse studies. Refinement of the inclusion and exclusion criteria allowed for a more focused review; however, the large exclusion criteria may limit the applicability of this review. The limited number of studies per polyphenol intervention is another key limitation of this review, which may have affected the overall findings and conclusions drawn from this review. Given the heterogeneous mix of studies included in this review, no cumulative statistical meta-analysis was conducted. This was due to the large diversity of polyphenols tested and variety of depression scales used. The lack of reported data on effect sizes is another important limitation of this review which affects both the meaningfulness and practical importance of these results. A narrative synthesis of the results has been provided, which comes with a risk of interpretation bias from the authors. Only published trials available on the preselected databases were available to be reviewed, which may have skewed the findings.

The review also highlighted a lack of research assessing polyphenols for depression in both men and young adults. Emerging research is beginning to highlight differences in which men and women express symptoms of depression; however, it still remains unclear if these differences affect treatment outcomes (72). Studies in young adults are also needed. Over 75% of mental health problems occur before the age of 25 y (73). According to the Australian Bureau of Statistics National Survey of Mental Health and Wellbeing: Summary of Results 2007, younger people were more likely to have a mental disorder than older people (74). The lack of studies on young adults and men included in this review limits the relevance of these findings to a broader audience.

In conclusion, to our knowledge, this was the first systematic literature review to assess the effects of polyphenols on the symptoms of depression. The review has identified a

strong foundation for suggesting that polyphenols do play an important role in the disorder. The inclusion of both observational and experimental designs has allowed for a comprehensive synthesis of both depression prevalence as well as intention-to-treat analysis. There appears to be a protective role of consuming higher amounts of polyphenols in reducing depression risk across several populations. In addition to the reduced prevalence, there also appears to be a therapeutic benefit of consuming certain polyphenols in reducing depressive symptoms. In the case of isoflavones this could be due to their phytoestrogen effect. Of the polyphenols included in this review, coffee and curcumin, soy isoflavones, tea and cocoa flavanols, walnut flavonols, citrus flavanones, and the stilbene resveratrol show the most promise and would be good candidates for future research. The review also identified that further research is required to investigate the role of polyphenols for depression in men and young adults. Additional studies are needed to confirm these findings.

Acknowledgments

The authors' responsibilities were as follows—JB: conducted the literature search, analyzed the data, and drafted the manuscript with edits from DS and JS; and all authors: designed the research question, developed the search terms, and read and approved the final manuscript.

References

1. Schmidt HD, Shelton RC, Duman RS. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. Neuropsychopharmacology 2011;36(12):2375–94.
2. Marcus M, Yasamy MT, van Ommeren M, Chisholm D, Saxena S. Depression: a global public health concern. Geneva: WHO; 2012.
3. McCall WV, Kintziger KW. Late life depression: a global problem with few resources. Psychiatr Clin North Am 2013;36(4):475–81.
4. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;71(2):171–86.
5. Jacka FN. Nutritional psychiatry: where to next? EBioMedicine 2017;17:24–9.
6. Foster JA, Neufeld K-AM. Gut–brain axis: how the microbiome influences anxiety and depression. Trends Neurosci 2013;36(5):305–12.
7. Angelino D, Godos J, Ghelfi F, Tieri M, Titta L, Lafranconi A, Marventano S, Alonzo E, Gambera A, Sciacca S, et al. Fruit and vegetable consumption and health outcomes: an umbrella review of observational studies. Int J Food Sci Nutr 2019;70(6):652–67.
8. Suzuki T, Miyaki K, Tsutsumi A, Hashimoto H, Kawakami N, Takahashi M, Shimazu A, Inoue A, Kurioka S, Kakehashi M, et al. Japanese dietary pattern consistently relates to low depressive symptoms and it is modified by job strain and worksite supports. J Affect Disord 2013;150(2):490–8.
9. Quirk SE, Williams LJ, O'Neil A, Pasco JA, Jacka FN, Housden S, Berk M, Brennan SL. The association between diet quality, dietary patterns and depression in adults: a systematic review. BMC Psychiatry 2013;13(1):175.
10. Sánchez-Villegas A, Delgado-Rodríguez M, Alonso A, Schlatter J, Lahortiga F, Majem LS, Martínez-González MA. Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. Arch Gen Psychiatry 2009;66(10):1090–8.
11. Opie R, Itsiopoulos C, Parletta N, Sanchez-Villegas A, Akbaraly TN, Ruusunen A, Jacka F. Dietary recommendations for the prevention of depression. Nutr Neurosci 2017;20(3):161–71.
12 Taylor AM, Holscher HD. A review of dietary and microbial connections to depression, anxiety, and stress. Nutr Neurosci 2018: 1–14.
13. Serra-Majem L, Trichopoulou A, de la Cruz JN, Cervera P, Álvarez AG, La Vecchia C, Lemtouni A, Trichopoulos D. Does the definition of the Mediterranean diet need to be updated? Public Health Nutr 2004;7(7):927–9.
14. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, Trichopoulos D. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr 1995;61(6): 1402S–6S.
15. Nestle M. Mediterranean diets: science and policy implications. Am J Clin Nutr 1995;61(6 Suppl):ixS–xS, 1313S–427S.
16. Pathak L, Agrawal Y, Dhir A. Natural polyphenols in the management of major depression. Expert Opin Investig Drugs 2013;22(7): 863–80.
17. Gomez-Pinilla F, Nguyen TT. Natural mood foods: the actions of polyphenols against psychiatric and cognitive disorders. Nutr Neurosci 2012;15(3):127–33.
18. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr 2000;130(8):2073S–85S.
19. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1):1.
20 The Joanna Briggs Institute. Checklist for quasi-experimental studies (non-randomized experimental studies) [Internet]. Adelaide: Joanna Briggs Institute; 2016. [Accessed 2019 Mar 25]. Available from: http://joannabriggs.org/research/critical-appraisal-tools.html.
21. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg 2014;12(12): 1500–24.
22. Sathyapalan T, Beckett S, Rigby AS, Mellor DD, Atkin SL. High cocoa polyphenol rich chocolate may reduce the burden of the symptoms in chronic fatigue syndrome. Nutr J 2010;9:55.
23. Bergman J, Miodownik C, Bersudsky Y, Sokolik S, Lerner PP, Kreinin A, Polakiewicz J, Lerner V. Curcumin as an add-on to antidepressive treatment: a randomized, double-blind, placebo-controlled, pilot clinical study. Clin Neuropharmacol 2013;36(3):73–7.
24. Nina Estrella RE, Landa AI, Lafuente JV, Gargiulo PA. Effects of antidepressants and soybean association in depressive menopausal women. Acta Pol Pharm 2014;71(2):323–7.
25. Atteritano M, Mazzaferro S, Bitto A, Cannata ML, D'Anna R, Squadrito F, Macrì I, Frisina A, Frisina N, Bagnato G. Genistein effects on quality of life and depression symptoms in osteopenic postmenopausal women: a 2-year randomized, double-blind, controlled study. Osteoporos Int 2014;25(3):1123–9.
26. Lopresti AL, Maes M, Maker GL, Hood SD, Drummond PD. Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study. J Affect Disord 2014;167: 368–75.
27. Sanmukhani J, Satodia V, Trivedi J, Patel T, Tiwari D, Panchal B, Goel A, Tripathi CB. Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial. Phytother Res 2014;28(4): 579–85.
28. Esmaily H, Sahebkar A, Iranshahi M, Ganjali S, Mohammadi A, Ferns G, Ghayour-Mobarhan M. An investigation of the effects of curcumin on anxiety and depression in obese individuals: a randomized controlled trial. Chin J Integr Med 2015;21(5):332–8.
29. Panahi Y, Badeli R, Karami GR, Sahebkar A. Investigation of the efficacy of adjunctive therapy with bioavailability-boosted curcuminoids in major depressive disorder. Phytother Res 2015;29(1):17–21.
30. Yu J-J, Pei L-B, Zhang Y, Wen Z-Y, Yang J-L. Chronic supplementation of curcumin enhances the efficacy of antidepressants in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. J Clin Psychopharmacol 2015;35(4):406–10.

31. Ibero-Baraibar I, Perez-Cornago A, Ramirez MJ, Martínez JA, Zulet MA. An increase in plasma homovanillic acid with cocoa extract consumption is associated with the alleviation of depressive symptoms in overweight or obese adults on an energy restricted diet in a randomized controlled trial. J Nutr 2016;146(4): 897S–904S.
32. Pribis P. Effects of walnut consumption on mood in young adults—a randomized controlled trial. Nutrients 2016;8(11):668.
33. Hirose A, Terauchi M, Akiyoshi M, Owa Y, Kato K, Kubota T. Low-dose isoflavone aglycone alleviates psychological symptoms of menopause in Japanese women: a randomized, double-blind, placebo-controlled study. Arch Gynecol Obstet 2016;293(3): 609–15.
34. Mirghafourvand M, Charandabi SMA, Hakimi S, Khodaie L, Galeshi M. The effect of orange peel essential oil on postpartum depression and anxiety: a randomized controlled clinical trial. Iran Red Crescent Med J 2017;19(2):e30298.
35. Kamalifard M, Khalili AF, Namadian M, Herizchi S, Ranjbar Y. Comparison of the effect of lavender and bitter orange on depression in menopausal women: a triple-blind randomized controlled trial. Int J Womens Health Reprod Sci 2017;5(3):224–30.
36. Davinelli S, Scapagnini G, Marzatico F, Nobile V, Ferrara N, Corbi G. Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: a randomized, placebo-controlled study. Maturitas 2017;96:77–83.
37. Kazemian A, Toghiani A, Shafiei K, Afshar H, Rafiei R, Memari M, Adibi P. Evaluating the efficacy of mixture of *Boswellia carterii*, *Zingiber officinale*, and *Achillea millefolium* on severity of symptoms, anxiety, and depression in irritable bowel syndrome patients. J Res Med Sci 2017;22(11):120.
38. Chang SM, Chen CH. Effects of an intervention with drinking chamomile tea on sleep quality and depression in sleep disturbed postnatal women: a randomized controlled trial. J Adv Nurs 2016;72(2):306–15.
39. Hintikka J, Tolmunen T, Honkalampi K, Haatainen K, Koivumaa-Honkanen H, Tanskanen A, Viinamäki H. Daily tea drinking is associated with a low level of depressive symptoms in the Finnish general population. Eur J Epidemiol 2005;20(4):359–63.
40. Niu K, Hozawa A, Kuriyama S, Ebihara S, Guo H, Nakaya N, Ohmori-Matsuda K, Takahashi H, Masamune Y, Asada M, et al. Green tea consumption is associated with depressive symptoms in the elderly. Am J Clin Nutr 2009;90(6):1615–22.
41. Chen X, Lu W, Zheng Y, Gu K, Chen Z, Zheng W, Shu XO. Exercise, tea consumption, and depression among breast cancer survivors. J Clin Oncol 2010;28(6):991–8.
42. Ruusunen A, Lehto SM, Tolmunen T, Mursu J, Kaplan GA, Voutilainen S. Coffee, tea and caffeine intake and the risk of severe depression in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. Public Health Nutr 2010;13(8):1215–20.
43. Li Y, Dai Q, Tedders SH, Arroyo C, Zhang J. Legume consumption and severe depressed mood, the modifying roles of gender and menopausal status. Public Health Nutr 2010;13(8):1198–206.
44. Lucas M, Mirzaei F, Pan A, Okereke OI, Willett WC, O'Reilly ÉJ, Koenen K, Ascherio A. Coffee, caffeine, and risk of depression among women. Arch Intern Med 2011;171(17):1571–8.
45. Feng L, Li J, Kua EH, Lee TS, Yap KB, Rush AJ, Ng TP. Association between tea consumption and depressive symptoms in older Chinese adults. J Am Geriatr Soc 2012;60(12):2358–60.
46. Feng L, Yan Z, Sun B, Cai C, Jiang H, Kua EH, Ng TP, Qiu C. Tea consumption and depressive symptoms in older people in rural China. J Am Geriatr Soc 2013;61(11):1943–7.
47. Omagari K, Sakaki M, Tsujimoto Y, Shiogama Y, Iwanaga A, Ishimoto M, Yamaguchi A, Masuzumi M, Kawase M, Ichimura M, et al. Coffee consumption is inversely associated with depressive status in Japanese patients with type 2 diabetes. J Clin Biochem Nutr 2014;55(2): 135–42.
48. Pham NM, Nanri A, Kurotani K, Kuwahara K, Kume A, Sato M, Hayabuchi H, Mizoue T. Green tea and coffee consumption is inversely associated with depressive symptoms in a Japanese working population. Public Health Nutr 2014;17(3):625–33.
49. Yu S, Guo X, Yang H, Zheng L, Sun Y. Soybeans or soybean products consumption and depressive symptoms in older residents in rural Northeast China: a cross-sectional study. J Nutr Health Aging 2015;19(9):884–93.
50. Li F-D, He F, Ye X-J, Shen W, Wu Y-P, Zhai Y-J, Wang X-Y, Lin J-F. Tea consumption is inversely associated with depressive symptoms in the elderly: a cross-sectional study in eastern China. J Affect Disord 2016;199:157–62.
51. Chang S-C, Cassidy A, Willett WC, Rimm EB, O'Reilly EJ, Okereke OI. Dietary flavonoid intake and risk of incident depression in midlife and older women. Am J Clin Nutr 2016;104(3):704–14.
52. Su Q, Yu B, He H, Zhang Q, Meng G, Wu H, Du H, Liu L, Shi H, Xia Y, et al. Nut consumption is associated with depressive symptoms among Chinese adults. Depress Anxiety 2016;33(11):1065–72.
53. Chan S-P, Yong P, Sun Y, Mahendran R, Wong J, Qiu C, Ng T-P, Kua E-H, Feng L. Associations of long-term tea consumption with depressive and anxiety symptoms in community-living elderly: findings from the Diet and Healthy Aging Study. J Prev Alzheimers Dis 2018;5(1): 21–5.
54. Navarro A, Abasheva D, Martínez-González M, Ruiz-Estigarribia L, Martín-Calvo N, Sánchez-Villegas A, Toledo E. Coffee consumption and the risk of depression in a middle-aged cohort: the SUN project. Nutrients 2018;10(9):1333.
55. Miyake Y, Tanaka K, Okubo H, Sasaki S, Furukawa S, Arakawa M. Soy isoflavone intake and prevalence of depressive symptoms during pregnancy in Japan: baseline data from the Kyushu Okinawa Maternal and Child Health Study. Eur J Nutr 2018;57(2):441–50.
56. Yu B, Yu F, Su Q, Zhang Q, Liu L, Meng G, Wu H, Xia Y, Bao X, Shi H, et al. A J-shaped association between soy food intake and depressive symptoms in Chinese adults. Clin Nutr 2018;37(3):1013–8.
57. Godos J, Castellano S, Ray S, Grosso G, Galvano F. Dietary polyphenol intake and depression: results from the Mediterranean Healthy Eating, Lifestyle and Aging (MEAL) study. Molecules 2018;23(5):999.
58. Mofrad MD, Siassi F, Guilani B, Bellissimo N, Azadbakht L. Association of dietary phytochemical index and mental health in women: a cross-sectional study. Br J Nutr 2019;121(9):1049–56.
59. Herge WM, Landoll RR, La Greca AM. Center for Epidemiologic Studies Depression Scale (CES-D). In: Gellman MD, Turner JR, editors. Encyclopedia of behavioral medicine. New York (NY): Springer; 2013. pp. 366–7.
60. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. J Psychosom Res 2002;52(2):69–77.
61. Zung WW, Richards CB, Short MJ. Self-rating depression scale in an outpatient clinic: further validation of the SDS. Arch Gen Psychiatry 1965;13(6):508–15.
62. Brown D. Do food frequency questionnaires have too many limitations? J Am Diet Assoc 2006;106(10):1541–2.
63. Lassale C, Batty GD, Baghdadli A, Jacka F, Sánchez-Villegas A, Kivimäki M, Akbaraly T. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. Mol Psychiatry 2019:24(7):965–86.
64. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. Ann Neurol 2013;74(4): 580–91.
65. Dias GP, Cavegn N, Nix A, do Nascimento Bevilaqua MC, Stangl D, Zainuddin MSA, Nardi AE, Gardino PF, Thuret S. The role of dietary polyphenols on adult hippocampal neurogenesis: molecular mechanisms and behavioural effects on depression and anxiety. Oxid Med Cell Longev 2012:541971.
66. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr 2004;79(5):727–47.
67. Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr 2005;81(1):230S–42S.

68. Akram M, Shahab-Uddin AA, Usmanghani K, Hannan A, Mohiuddin E, Asif M. Curcuma longa and curcumin: a review article. Rom J Biol Plant Biol 2010;55(2):65–70.
69. Nagpal M, Sood S. Role of curcumin in systemic and oral health: an overview. J Nat Sci Biol Med 2013;4(1):3.
70. Chauhan M, Saha S, Roy A. Curcumin: a review. J Appl Pharm Res 2014;2(1):18–28.
71. Ferruzzi MG. The influence of beverage composition on delivery of phenolic compounds from coffee and tea. Physiol Behav 2010;100(1):33–41.
72. Weissman MM. Treatment of depression: men and women are different? Am J Psychiatry 2014;171(4):384–7.
73. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62(6):593–602.
74. Slade T, Johnston A, Oakley Browne MA, Andrews G, Whiteford H. 2007 National Survey of Mental Health and Wellbeing: methods and key findings. Aust N Z J Psychiatry 2009;43(7): 594–605.